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PATENT
Attorney Docket No.: PHO 107-DIV

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

RECEIVED

In re application of:

DEES et al.

Serial No.: 09/382,622

Filed: August 25, 1999

Examiner: G. Gabel

Art Unit: 1641

For: High Energy Phototherapeutics
Agents

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Robert M. Gandy

Date: January 9, 2001

JAN 18 2001

Information Disclosure Statement Regarding Inventorship

Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants call the attention of the Examiner to the following facts which relate generally to inventorship and the relation of the named Dees et al inventors (of Photogen) to Dr. Gerald L. Wolf. Litigation styled as Photogen, Inc. v. Gerald L. Wolf was filed on September 22, 2000 in the Northern District of Illinois (Civil Action 00C 5841, Judge Moran) which, among other things, requests a declaration that Dr. Gerald Wolf is not an inventor of the invention in the instant patent application. See Attachments 1 (Complaint) and 59 (Amended Complaint). As of this writing, neither the original nor the amended complaint has been answered.

Similar information disclosures have been submitted in the parent application, where method claims were elected for prosecution. In this divisional application, composition or structure claims

are being prosecuted. Until December 4, 2000, when Dr. Wolf orally addressed the board of directors of Photogen, the assignee of this application, it was not clear just what inventorship assertions were being made by Dr. Wolf. In his December 4, 2000 address, Dr. Wolf seemed clearly to disavow any assertion of joint inventorship in the substance claimed in claim 1 of this application. The relevant text is presented below.

Even though Dr. Wolf has apparently disavowed participation in inventorship of this application, the Examiner should be made aware of the dispute and the relationship between Photogen and Dr. Wolf. The attached documents include several communications where inventorship was raised. Applicants are unaware of whether Dr. Wolf (or his prior employer) has filed any competing applications naming himself as an inventor and/or copied any claims into any such application for interference purposes. Regardless, in view of MPEP Chapter 2000, Applicants call to the Examiner's attention these facts and issues in the attached Complaint and other documents.

I. Background and Relationship of Photogen to Dr. Wolf

a. Identification of Parties

As will be explained further herein and in the accompanying copy of the Complaint of Attachments 1 and 59, in 1998 Photogen first met with Dr. Wolf and later entered into a contract with his employer at that time, Massachusetts General Hospital ("MGH"), also known as "The General Hospital Corp.," wherein Dr. Wolf became the named Principal Investigator of a sponsored research project to work on certain inventions that had previously been conceived by one or more of the named inventors herein. All but one of the named inventors are Ph.D. scientists formerly with the Oak Ridge National Laboratory who became founders and employees of Photogen. The sole

exception is John Smolik (also named as a co-inventor) who at the relevant times was an officer of Photogen and is trained as a chemical engineer. Dr. Wolf is not named as a co-inventor on this patent application.

B. The Prior Information Disclosure Statement and The License

As disclosed to the PTO in an information disclosure statement mailed April 6, 2000, during the course of the sponsored research, at least one of the named inventors herein received a copy of an invention disclosure document from Dr. Wolf prior to filing the parent of the instant application. On belief, Dr. Wolf's disclosure did not disclose or suggest the invention(s) at issue in the present application. Dr. Wolf's disclosure was furnished to Photogen only after Photogen had advised Dr. Wolf (subject to a confidentiality agreement) of the subject of the instant application and of Photogen's intention to file a patent application on the subject.¹ MGH was Dr. Wolf's employer at the time that Dr. Wolf made his disclosure. MGH subsequently filed (and is currently prosecuting) a U.S. patent application for Dr. Wolf concerning that same Wolf invention disclosure (the "MGH patent application"). On information and belief, the MGH patent application received a serial number of 09/183,166 and a filing date of October 29, 1998. On information and belief, that application has been abandoned in favor of a continuation.

Relying on certain representations of Dr. Wolf, Photogen acquired from MGH exclusive license rights within a certain field under that MGH patent application, and Photogen has been underwriting (but not controlling) the worldwide prosecution costs of that application. That underlying U.S. application (by Dr. Wolf as the sole named inventor) provided the basis for a PCT filing (Wolf et al.) which was eventually published on May 11, 2000 as WO 00/25819, entitled

¹ Applicants do not believe that Dr. Wolf's disclosure discloses the subject matter of the instant application. Nor does it disclose halogenated xanthenes, on information and belief.

"Enhanced Radiation Therapy," a copy of which is enclosed as Attachment 2. A related published PCT application WO 00/25829 (McIntire et al.) entitled "Radiodense Compositions" has the same publication date and is enclosed as Attachment 3. It can be seen that each of these PCT applications is in the name of MGH and Nycomed Imaging. From the published PCT applications, it can be seen that the earliest underlying U.S. application bears USSN 09/183,166 filed October 29, 1998. The PCT applications purport to be continuations or CIPs of USSN 09/183,166 and USSN 60/131,418 filed April 28, 1999. The Examiner is invited and encouraged to review the disclosures of the attached published MGH applications as well as the pending (and parent) U.S. applications.

C. Photogen Activities Before Meeting with Dr. Wolf

Beginning in October 1996, Photogen began filing patent applications concerning photodynamic therapy (PDT) and especially concerning their discoveries involving the ability to have two (or more) photons excite an agent through a virtual quantum mechanical level to an activated or excited state, following which a therapeutic effect and/or imaging could occur. *See, e.g.,* Fisher, Wachter, and Dees U.S. Patent Nos. 5,829,448; 5,998,597; and 6,042,603; and Wachter, Fisher, and Dees U.S. Patent No. 5,832,931 (Attachments 4-7). One aspect of this technology involves administering a photoactive agent to a patient or diseased tissue and then applying energy in a controlled fashion to cause the desired effect to occur, be it therapeutic or imaging or both. Photogen was interested in locating a source of expertise in directing the application of energy to diseased tissue – specifically for improving on how to direct an energy source to a cancer or tumor. It was to this end that Photogen met with Dr. Wolf, who was at MGH and was Director of MGH's Center for Imaging and Pharmaceuticals Research.

In addition, and as set forth in the accompanying Complaints, long before the first meeting with Dr. Wolf, Photogen had been studying a number of the halogenated xanthenes, including Rose

Bengal, for various purposes. Photogen already knew that Rose Bengal (which Photogen referred to under the code name "PH-10") was useful as a therapeutic and diagnostic agent and wanted to conduct further studies on it as a PDT agent. Photogen also was looking at other technologies and energy sources in connection with its research, as related in the Complaints. Photogen knew, for example, about efforts of a well-known company in Photogen's field of PDT, namely Pharmacyclics, Inc., to use certain PDT agents (not halogenated xanthenes) for radiosensitization. This was publicly known in 1996. Photogen, and particularly the named inventors, were aware of this work and the interaction of ionizing radiation with heavy atoms well prior to the first meeting with Dr. Wolf. Pharmacyclics received issued U.S. patents in this "PDT agent + radiation" area in 1997, *e.g.* Hemmi et al. U.S. 5,591,422 issued January 7, 1997, which states in at least the Abstract that "texaphyrin metal complexes ... are useful for localization, radiosensitization, and radiation therapy." (Attachment 8) Photogen had access to "Lutetium Texaphyrin" which is one of the members of the family of texaphyrins recited in the Pharmacyclics patent. *See also*, Young et al., "Gadolinium (III) texaphyrin: A Tumor Selective...Radiation Sensitizer That Is Detectable By MRI," Proc. Nat'l Acad Sci., Vol. 93, pp. 6610-15 (June 1996) (Attachment 9) and a subsequent article commenting on it, Bernhard et al., "Re-Evaluating Gadolinium (III) Texaphyrin as a Radiosensitizing Agent," Cancer Research 60, 86-91 (Jan 2000) (Attachment 10).

Another example of known technology came from Pacific Pharmaceuticals, which Photogen was studying before meeting with Dr. Wolf. *See* Kahl *et al.* U.S. Patent 5,654,423 (Attachment 11) issued on August 5, 1997, concerning compounds useful therapeutically in PDT, in boron neutron capture therapy as well as for MRI (medical resonance imaging) contrast enhancement. The material discussed there is a boronated porphyrin PDT agent, colloquially referred to as "BOPP." *See also* the earlier Kahl *et al.* U.S. Patent Nos. 5,284,831 and 5,149,801. (Attachments 12 and 13). These

Kahl *et al.* patents were issued to the University of California. Photogen, presumably like other PDT companies, was considering the use of PDT agents with other forms of radiation, namely ionizing radiation. This was well prior to any meetings or communications between Dr. Wolf and Photogen.

D. The First Meeting With Dr. Wolf

The first Photogen-Wolf meeting occurred for about 1.5 hours on May 28, 1998. Photogen's participants in this first meeting were Dr. Tim Scott, Dr. Craig Dees, and John T. Smolik. No confidentiality agreement or non-disclosure agreement was in place at the time of this meeting. At this first meeting, Dr. Wolf described in general terms the work that he was doing. He mentioned use of a focused microwave array to kill glandular material in breast tissue before it becomes cancerous (without mention of radiosensitizers). Dr. Wolf seemed to be unaware of PDT in general, and Photogen showed him a slide of a gel block which illustrated its two photon excitation ("TPE") invention. Photogen mentioned that one PDT agent it was studying was "PH-10." The participants discussed liposome delivery, which was a commonly-known delivery mechanism for drugs. Dr. Wolf mentioned using micelles, a general administration technique for delivery. (Dr. Dees had already worked with micelles for about 20 years, *see, e.g.* US patent nos. 4,599,227 ([Attachment 53](#)) and 5,128,139 ([Attachment 54](#)) in which Dr. Dees is listed as an inventor.) Given Photogen's interest in studies of PH-10 for therapy, Dr. Wolf mentioned that useful models for study could be prostate cancer in dogs and lung cancers in rabbits. He mentioned that his favorite tumor-finding agent for imaging was iohexol (a well known imaging contrast agent), and that it could be used for computerized tomography (CT) contrast. Iohexol, which is well known and not a halogenated xanthene, is the reference material against which all other CT contrast agents are compared and was already FDA approved. The whole discussion of Dr. Wolf's work with iohexol concerned imaging,

not treatment or therapeutics. Dr. Wolf described the chemical structure of iohexol and gave Photogen a small quantity of iohexol to see whether it was photoactive by Photogen's laser techniques. Dr. Wolf also advised Photogen what his time would cost if he were to undertake an assignment from the company. Photogen recalls that there was no discussion at this time with Dr. Wolf of any potential use of PH-10 as a radiopaque or radiosensitizer agent. Neither the chemical composition nor the structure of PH-10 was discussed with Dr. Wolf, and Dr. Wolf was not told at this meeting by Photogen that PH-10 was Photogen's code name for Rose Bengal.

E. Photogen's Experimental Confirmations

Before returning for a second meeting with Dr. Wolf, Photogen had already experimentally proven that Rose Bengal was radiopaque and had used it as a radiosensitizer with x-rays to kill cells. Also prior to this second meeting, Dr. Scott prepared an initial draft statement of the work for Dr. Wolf pursuant to the sponsored research project under discussion between Photogen and MGH. The work was to be directed primarily to CT-guided PDT using Rose Bengal as a PDT agent. The draft document noted that Rose Bengal is x-ray opaque.

F. The Second Meeting With Dr. Wolf

The second Photogen-Wolf meeting occurred on July 7, 1998 as the parties moved closer to a sponsored research agreement between Photogen and MGH. At that time, a confidential disclosure agreement was signed by Photogen and Dr. Wolf (Attachment 14, also included as Tab A of Attachment 1). At the second meeting, Photogen disclosed that Rose Bengal is radiopaque, and thus that iohexol (the radiopaque agent that Dr. Wolf was most familiar with) would not be needed as an imaging tool. Photogen proposed that Dr. Wolf test Rose Bengal as a PDT agent in an animal model. Dr. Wolf did not ask whether Rose Bengal had any therapeutic effect with radiation. Photogen

presented the draft statement of work to Dr. Wolf during this meeting. Following the meeting, Photogen shipped a supply of Rose Bengal to Dr. Wolf's lab for his investigations.

G. The Sponsored Research Agreement

On October 1, 1998, following these above-mentioned meetings and further correspondence and communications, Photogen and MGH entered into a sponsored research agreement (Attachment 17, also included as Tab B of Attachment 1). The protocol specifying the research to be conducted was directed to a "combination of two photon excitation photodynamic therapy (TPE-PDT) with advanced tumor imaging technology for the treatment of lung and prostate cancer." However, that protocol, which specified Dr. Wolf's first assignment, specifically mentions various work with PH-10. The protocol mentions, among other things, that the pharmacokinetics of PH-10 for concentration in target cells following systematic or interstitial administration is to be determined, advises that PH-10 is x-ray opaque, reasonably lipophilic, and may preferentially stain membranes of fast growing cells such as are found in tumors, that if injected into a tumor, PH-10 should display much different pharmacokinetics than iohexol, and that it is possible that PH-10 will enhance the effects of x-rays in killing tumor cells.

During the course of this sponsored research, Dr. Wolf at MGH initially worked with a CT machine to see how easily Rose Bengal could be detected. At Dr. Scott's direction to use an alcohol solvent, Dr. Wolf dissolved Rose Bengal in octanol (on belief) and took CT scans of test tubes with Rose Bengal solution in them. He proceeded to characterize how Rose Bengal distributed in the bodies of rabbits and tried to find ways to keep the Rose Bengal in the body for a longer time. At Photogen's direction, Dr. Wolf used a formulation of 10% Rose Bengal in saline with direct intratumoral injection, which gave very encouraging results. In late 1998 and early 1999, Photogen directed Dr. Wolf to perform experiments on Rose Bengal as a radiosensitizer, a path of research that

was accounted for in the statement of work for the project. Specific tasks performed by Dr. Wolf were injecting Rose Bengal directly into human tumors implanted in mice and then CT imaging the tumors using x-rays, measuring the retention of the Rose Bengal in the tumors over time, and working on protocols to allow radiation therapy on “MeWo mice” (mice with implanted radiation resistant melanoma tumors) using Rose Bengal as a radiosensitizer.

H. Photogen’s Subsequent Employment of Dr. Wolf, and His Inventorship Assertions

Dr. Wolf eventually left MGH to become an employee of Photogen. His employment agreement dated July 1, 1999 (Attachment 25, also included at Tab C of Attachment 1) contains a series of exhibits. On one of them (“Exhibit C -- Employee’s Intellectual Property”), Dr. Wolf listed his interests in relevant patents and patent applications and thereby represented that except as listed therein, he had no royalty, development, or similar compensation rights in the field, where he was a sole or joint inventor. Notably, he did not then assert (through any arrangement with MGH he might have had, or otherwise) any claim of joint inventorship in Photogen’s inventions, including those involving PH-10.²

Over the past several months, however, Dr. Wolf has asserted that he is a joint inventor of various Photogen subject matter. Because of this, Photogen, Dr. Wolf, and MGH had a meeting in June 2000, with each party represented by its own counsel. Dr. Wolf apparently desired to be named as a co-inventor with Photogen employees on one or more Photogen inventions that concern Rose Bengal and other halogenated xanthenes and their uses. Dr. Wolf has not come forth with

² But see his prior communications of April 6, 1999 and May 3, 1999 (Attachments 22, 24, *infra*).

documentation or other corroboration about inventorship and, in fact, it has been difficult for Photogen to determine just what Dr. Wolf thinks the facts to be at any given moment.

On belief, Dr. Wolf credits himself with disclosing the radiosensitization field in general to Photogen. However, while there appears to be a factual dispute about when Dr. Wolf made any disclosures to Photogen and the substance of disclosures, Photogen and its scientists: (1) previously knew about radiosensitization from work being done by others,³ (2) knew of halogenated xanthenes from previous work (and independently conceived of using halogenated xanthenes for radiosensitization), and (3) do not consider that Dr. Wolf participated in the conception of the claimed subject matter. Photogen understands the law to be that where one discloses what is publicly known elsewhere, that person does not thereby become a joint inventor with those who apply that knowledge. See Hess v. Advanced Cardiovascular, 106 F.3d 976, 41 USPQ2d 1782 (Fed.Cir. 1997). In this instance, the uses of iodine-containing molecules for radiosensitization was in the published literature long prior to even the first meeting with Dr. Wolf, and that art has been made of record herein. See, for example, Norman et al, "Iodinated Contrast Agents for Brain Tumor Localization and Radiation Dose Enhancement" (of record).⁴

Dr. Wolf apparently also considers that he is entitled to be a named inventor on matters where he participated in a reduction to practice. Even if Dr. Wolf may have assisted in reducing various Photogen inventions to practice, Applicants believe that the case law and the MPEP are to the contrary, and that conception is the touchstone of inventorship. MPEP §2137.01, at 2100-79

³ See, e.g., *supra* regarding the work by Pharmacyclics' and by Pacific Pharmaceuticals.

⁴ As we explained in the prosecution of parent application USSN 09/216,787, Norman's method is much more complex than described here, has serious disadvantages to it and does not disclose nor affect the patentability of the present application.

(Feb. 2000 Rev. 1); CR Bard v. M3, 48 USPQ2d 1225, 1222-23 (Fed.Cir. 1998); In re Hardee, 223 USPQ 1122, 1123 (Comm'r Pat. 1984) (cited in MPEP).

As noted above, Photogen, MGH, and Dr. Wolf have sought since June 2000 to arrive at some amicable resolution of their differences. At no time did Photogen or its named inventors ever believe that Dr. Wolf was an unnamed or non-joined co-inventor of the subject matter of the above-captioned patent application. Indeed, Photogen's proposal for resolution would not have included Dr. Wolf's name on any applications without a clear factual basis for doing so. Unfortunately, the parties were not able to reach an amicable resolution, and Photogen filed suit against Dr. Wolf. As noted above, an Amended Complaint (Attachment 59) has been filed, adding MGH as a defendant and correcting some factual averments. The factual background concerning the relationship with Dr. Wolf appears at paragraphs 1-10 and 18-67. Count VI of the lawsuit (Attachment 59 at page 22) seeks a declaratory judgment that, among other things, Photogen has correctly named the joint inventors in its patent applications and that Dr. Wolf is not a co-inventor. No discovery has yet occurred in the suit, nor has an answer to the complaint been filed.

Counsel for Dr. Wolf has never written to Photogen to state what role Dr. Wolf allegedly had in the conception of the subject matter claimed herein.

On belief, as of June 2000, Dr. Wolf was asserting that he suggested the broad notions of administering a radiosensitizer and then subjecting it to x-rays (or other ionizing radiation). (Compare this to his statement of the issue on Feb. 28, 2000, Attachment 34, *infra*.)

II. Dr. Wolf's December, 2000 Statement

On December 4, 2000, Dr. Wolf personally addressed Photogen's board of directors at a meeting in Chicago. Dr. Wolf consented to having his remarks tape-recorded. The following is an excerpt of a transcript of those recorded comments as prepared by Photogen's counsel. In these comments, Dr. Wolf refers to "PHO-107," which is the attorney docket number for the parent application of above-captioned patent application file. He also refers to "PH-10" which is a Photogen designation for Rose Bengal:

[Dr. Wolf] "So let's first look at the issues surrounding the patent protection for PH-10. I think that I can demonstrate that all I ever did was raise issues about the listing of the proper inventors. Raising these issues in the interest of Photogen is a responsibility of an employee and an officer and clearly not a breach of my contract. My position is summarized in my letter to Ted Grippo of May, 2000.⁵

"To set the stage for how I became involved with Photogen and the radiosensitization field, I will note that each side was quick to recognize the similarity between the special absorption of light to perform photodynamic therapy, as was Photogen's main preoccupation, and the focal absorption of x-ray energy to improve radiation therapy, which had been topic of serious investigation in my laboratory well before Photogen was formed. As the collaboration of all, it was always about a very special molecule identified by Photogen. I'll say that again. A very special molecule identified by Photogen.⁶ It falls in the class of small lipid-soluble molecules that were tested in my experiments. And that molecule is used with the methods that were covered in my research and my patent.⁷ This understanding of this collaboration is evident in John Smolik's letter of 10/13/98, wherein Photogen sought to

⁵A copy of that May 4, 2000 letter is submitted to the PTO as Attachment 52 hereto.

⁶On belief, Dr. Wolf is referring to halogenated xanthenes, and in particular Rose Bengal.

⁷On belief, Dr. Wolf's reference to "my patent" is a reference to USSN 09/183,166 which is mentioned as the earliest priority document in the PCT published application on behalf of Wolf et al., entitled "Enhanced Radiation Therapy," submitted as Attachment 2.

merge their own compound with my method. Let's take a look at that, which is the next one in your handout.⁸

"First, I highlighted the date of October 13th because the sponsored Research Agreement⁹ began October 1st and was fully in effect. John says,¹⁰ 'I learned from Dr. Wolf of his area-- of his work in the area of x-ray photosensitization.' John says, 'Photogen has identified a compound.' That compound is the unique contribution that you guys made. He then says 'Dr. Wolf has prepared an invention disclosure that addresses the process' in other words the method 'of x-ray photosensitization.' And goes on that says that they would like to fund the preparation and filing of the new patent and obtaining the rights to this invention. Now because PH-10 is actually a very well-known molecule, method patents showing the value of this molecule specifically are important. This marriage, PH-10 from Photogen with my methods, is the real reason for my employment agreement and for the evolution of the sponsored research at MGH. I believe that for the maximum protection of PH-10, my methods needed to be included in the important patent filings for the radiosensitization with PH-10. Thus, it was a complete surprise to me that Photogen secretly and independently filed patent claims incorporating the methods and the physical basis for the effects included in my confidential disclosures to them. It was especially surprising that they withheld these patents from me for my -- for the entire period of our collaborative research and even for 6 months after I became Medical Director.

"Let's next apply the same scrutiny to PH-107, which was filed December 16th of '98.¹¹ I have circled two claims in this patent. The date is important because it happened after Photogen got the copies of our confidential disclosure.¹² Claim 1 is to a radiosensitizer agent -- a material, a halogenated xanthene. I have said that we have never, ever disputed that Photogen was responsible for identifying this unique agent, but the Patent Office asked Photogen to restrict their claims. What this basically means is the Patent Office says we're

⁸ A copy of the October 13, 1998 letter is enclosed as Attachment 60.

⁹ The sponsored Research Agreement is submitted as Attachment 17.

¹⁰ Notwithstanding the quotation marks, Dr. Wolf appears to be paraphrasing here rather than quoting statements by Mr. Smolik or others.

¹¹ Dr. Wolf must mean PHO-107, which was filed on December 21, 1998.

¹² Photogen alerted the PTO to the receipt of that disclosure in their Information Disclosure Statement mailed April 6, 2000.

having trouble evaluating all the claims, why don't you pick one and put that forward as the one that you want to consider to be the main claim of this patent, and they picked 31. Let's look at what 31 says. 31 says 'a method' -- not a material as John Smolik said in his letter, but a method, which John has already ascribed as having originated in my work at MGH. If you then follow everything that's in this method with the exception of the radiosensitizer, it is all my work.

"Claim 31 is clearly a method. This is the same method that Smolik indicated that he wanted MGH to confidentially disclose to Photogen, and which Photogen did not disclose to the Patent Office. In other words, they failed the duty of candor when they filed this patent. PH-107, Photogen 107 may not be enforceable because the patent as filed does not meet the duty of candor unless I am added as inventor of the claim[ed] methods. A patent must issue on application of the correct inventors. In other words, if you don't list the inventors correctly, your patent is invalid.

"I believe that the data shows that the method originated from MGH before you got involved. I believe if you're going to file method patents, you will have to include the inventor of those method patents (a) to avoid having your patents invalidated and (b) to strengthen the position that you have. If you file for methods and have not included the people that invented those methods, it can be shown that you were confidentially disclosed those methods, you're in deep do-do. The only way that you can do that, in my opinion, is that you have to make peace with MGH. Now let's see if we can figure out what is your peace initiative with MGH. First of all, Photogen approached MGH and say [*sic*, said], 'We love you. You're man's greatest hospital. You've got one of the best inventors in the world. We want to work hand-in-glove with you.' Then you secretly patented work that you learned from them. Then you deny that you had anything whatsoever to do with radiosensitization experiments.¹³ Then you file suit against their star inventor and said, 'We hope that we don't have to file suit against you,' and then you took away the data that they told you doesn't belong to you and

¹³ We believe that the denial Dr. Wolf refers to is a misstatement in Photogen's original complaint in the case pending against him. If there ever was any such denial, as Dr. Wolf indicates, that denial has been superseded by revised and clarified allegations of the Amended Complaint (Attachment 59). Paragraph 29 of the Amended Complaint explains that Protocol 1 promulgated simultaneously with the sponsored Research Agreement of October 1, 1998 specified Dr. Wolf's first assignment. The protocol specifically mentions various work with PH-10. The protocol mentions, among other things, that the pharmacokinetics of PH-10 for concentration in target cells following systematic or interstitial administration is to be determined, advises that PH-10 is x-ray opaque, reasonably lipophilic, and may preferentially stain membranes of fast growing cells such as are found in tumors, that if injected into a tumor, PH-10 should display much different pharmacokinetics than iohexol, and that it is possible that PH-10 will enhance the effects of x-rays in killing tumor cells.

you have to return it immediately.¹⁴ Now this is the way that Richard Nixon negotiated peace with Hanoi. I don't think that's a good way to get MGH to cooperate with you. And I also point out that PH-107 and [another Photogen application file] are not yours because they originated before the sponsored agreement started.¹⁵ So you will have to negotiate with MGH to give you the license on that if in fact you believe me when I tell you that because of you knowing about the methods and having filed a method patent, you're going to have to go the MGH to get that done.”

[emphasis added].

Thus, it will be understood that Dr. Wolf, so far as the PHO-107 application(s) are concerned, is asserting that he is a co-inventor of the method of claim 31. Dr. Wolf emphasized that “we” (presumably himself and either his counsel or his former employer MGH) never disputed that Photogen alone was responsible for identifying PH-10 as a radiosensitizer agent. And while Photogen vigorously disagrees with Dr. Wolf’s assertion that he should be named as a joint inventor of the method claims, since those method claims have been canceled from this application,¹⁶ both Photogen and Dr. Wolf appear to be in agreement that the correct inventive entity of the non-method claims does not include Dr. Wolf. No discussion should be needed here on the inventorship issue for the method claims.

¹⁴Photogen terminated Dr. Wolf and his staff. Thereafter, Photogen found various data left by Dr. Wolf and his staff in Photogen’s offices. On information and belief, data that could be identified as belonging to MGH and Tufts was promptly turned over to MGH and Tufts, respectively, by Photogen.

¹⁵Photogen acknowledges that it began a relationship with Dr. Wolf prior to formal signing of the sponsored research agreement. For example, Photogen shipped a quantity of PH-10 to Dr. Wolf and had various discussions with him, many of which are related in the prior Information Disclosure Statement. This earlier relationship does not make Dr. Wolf a joint inventor.

¹⁶The Patent Application Transmittal under Rule 60b directed the cancellation of claims 31-50 and 53. In the first Office Action, the Examiner indicated that claims 1-30, 51 and 52 were pending.

III. The Accompanying Documentation

To inform the PTO of possible assertions by Dr. Wolf and the relationship of Photogen to him and to MGH, attached hereto are selected communications to, from, or concerning Dr. Wolf. Other than named co-inventors (Drs. Dees, Scott, Wachter and Mr. Smolik) and Dr. Wolf, further persons or organizations referenced in these attachments include:

- T. Grippo, one of the counsel for Photogen
- M. Murphy, another counsel for Photogen
- E. Manzo, the undersigned counsel for Photogen
- "CAMMCM," the acronym for the law firm of Messrs. Manzo and Murphy, et al.
- P. Fasse, patent counsel for Mass. General Hospital (MGH)
- Iain Miller, an administrator at MGH

The attachments comprise:

1. Complaint: *Photogen v. Gerald L. Wolf*
 - Tab A. Confidential Disclosure Agreement
 - Tab B. Research Agreement of October 1, 1998
 - Tab C. Employment Agreement
2. MGH + Nycomed published patent application (May 11, 2000), WO 00/25819, entitled "ENHANCED RADIATION THERAPY" by Wolf et al.
3. MGH + Nycomed published patent application (May 11, 2000), WO 00/25829, entitled "RADIODENSE COMPOSITIONS" by McIntire et al.
4. Photogen U.S. Patent No. 5,829,448 (Fisher, Wachter, and Dees)
5. Photogen U.S. Patent No. 5,998,597 (Fisher, Wachter, and Dees)
6. Photogen U.S. Patent No. 6,042,603 (Fisher, Wachter, and Dees)
7. Photogen U.S. Patent No. U.S. Patent No. 5,832,931 (Wachter, Fisher, and Dees)

8. Pharmacyclics U.S. Patent 5,591,422 issued January 7, 1997 (Hemmi et al.)
9. Young et al., "Gadolinium (III) texaphyrin: A tumor selective...radiation sensitizer that is detectable by MRI," Proc. Nat'l Acad Sci., Vol. 93, pp. 6610-15 (June 1996)
10. Bernhard et al., "Re-Evaluating Gadolinium (III) Texaphyrin as a Radiosensitizing Agent," Cancer Research 60, 86-91 (Jan 2000)
11. Kahl *et al.* U.S. Patent 5,654,423 issued August 5, 1997
12. Kahl *et al.* U.S. Patent Nos. 5,284,831 issued Feb. 8, 1994
13. Kahl *et al.* U.S. Patent Nos. 5,149,801 issued Sept. 22, 1992
14. July 7, 1998 Confidential Disclosure Agreement (also attached to the Complaint of Attachment 1 at Tab "A")¹⁷
15. August 24, 1998 Dr. T. Scott letter to Dr. Wolf indicating, pursuant to the nondisclosure agreement, Photogen's sensitive ideas that have been discussed. This listing includes (1) using Rose Bengal as an agent for PDT, (2) as an x-ray contrast agent, (3) as an x-ray sensitizer for cancer treatment, (4) for possible use x-ray fluorescence-imaging, (5) the modification of Rose Bengal for targeting and enhanced response to the previously listed topics, and a sixth topic.
16. August 25, 1998 Dr. Wolf's response, listing MGH's sensitive ideas (redacted). While redacted, the words "Rose Bengal" do not appear in the document, nor do the words "halogenated xanthene." Dr. Wolf states, "The best outcome is that we jointly develop truly [*sic*] and fully protected intellectual property. I believe the final agreement will alloww [*sic*] us to do that."
17. October 1, 1998 Research Agreement (also attached to the Complaint of Attachment 1 at Tab "B")
18. Oct 13, 1998 Dr. Wolf memo to MGH (confidential material about "Company A" redacted.) Referring to Photogen as "Company B," Dr. Wolf asserts that "the radiodense adjuvant field was confidentially disclosed to Company B" on July 7, 1998 in the context of a sponsored research agreement. He also asserts that Company B has prepared a patent filing as to which "the MGH invention disclosure has temporal and intellectual priority."¹⁸

¹⁷ It should be noted that this confidentiality agreement was extended in November 1998 to cover radiodense adjuncts for radiation therapy.

¹⁸ Here, Dr. Wolf appears to be referring to the Wolf-MGH '166 patent application under which Photogen is an exclusive licensee. Interestingly, Dr. Wolf's interpretation of events up to this date is that he disclosed the subject matter of the Wolf-MGH '166 patent application to Photogen, but he does not suggest that Photogen has any

19. Dec. 8, 1998 Dr. Scott letter to Dr. Wolf, noting that Photogen wishes to license Dr. Wolf's MGH patent application and use this in combination with Photogen's patent.
20. Dec. 8, 1998 Dr. Wolf memo responding to Dr. Scott's memo of 8 Dec, expressing willingness to meet and "discuss the patent situation for the radiation therapy enhancement."
21. April 5, 1999 Dr. Wolf memo to John Smolik, mentioning that Dr. Wolf "... already [has] patent applications for use of radiopaque materials to diagnose or treat diseases that are unavailable to you or that you have declined to license."¹⁹
22. April 6, 1999 Dr. Wolf memo to John Smolik, asserting, "**Photogen has filed claims in the radiodense area which clearly came from our discussions, were shown you with materials labelled Confidential, and are covered by our confidential disclosure agreement signed 6/30/98 [sic].**"
23. April 13, 1999 Photogen's press release announcing Photogen's discovery of a chemical compound, that is already widely used, that also acts as a radiosensitizer for use with x-rays to destroy abnormal cells.
24. May 3, 1999 Dr. Wolf memo to John Smolik, discussing his ideas for joining Photogen and asserting, "In addition, the company has apparently filed new patents for radiation enhancement with materials known to you and has announced and expanded **my discovery** that rose bengal, when injected intratumorally, has an exceptional concentration and retention in tumors." [emphasis added]
25. July 1, 1999 Employment agreement (also attached to the Complaint of Attachment 1 at Tab "C") containing as Exh. C thereto "Employee's [Wolf's] Intellectual Property" listing Dr. Wolf's inventions but not including anything involving PH-10.
26. Feb. 7, 2000 Dr. Wolf memo to Dr. T. Scott re "patent filings for radiodense adjuvants" (PHO-107). Dr. Wolf has reviewed prior patent filings provided by Dr. E. Wachter. Among other things, Dr. Wolf charges a "violation" ("**The subject matter of these ... appear to violate the prior work done at MGH and confidentially disclosed to Photogen about 6 months before these filings. The subject matter also appears to have claims that may have been anticipated by separate filing by Nycomed**"). Dr. Wolf announces that he has taken the "notebooks covering PH-10 research conducted at MGH

significant intellectual property of its own. Dr. Wolf still had not realized the significance and usefulness of Rose Bengal as a radiosensitizer, despite Photogen's repeated attempts to inform him on this. One may wonder how he could assert joint invention in subject matter that he did not yet comprehend.

¹⁹ Photogen is not presently aware of pending U.S. applications of Dr. Wolf other than the '166 application and a continuation thereof.

during the summer of 1998 to a secure location” and requests that Photogen’s Board of Directors be notified and an “independent review” be conducted.

27. Feb. 7, 2000 Dr. Scott response to Dr. Wolf memo of 7 Feb, acknowledging receipt and indicating that the company’s patent lawyers (Manzo et al.) will be contacted for advice.
28. Feb. 8, 2000 Dr. Wolf response to Dr. Scott memo of 7 Feb, stating “My reasons for wanting to resolve the issues are to obtain clear Photogen title to PH-10 for the remaining development effort, since this material seems so key to our efforts to use x-ray photons for PDT.”
29. Feb 14, 2000 Dr. Scott letter to Dr. Wolf requesting a list of specific concerns Dr. Wolf has regarding intellectual property. Dr. Scott recites MPEP guidance regarding inventorship (i.e., inventorship based solely on conception).
30. Feb 14, 2000 Dr. E. Wachter memo to Dr. C. Dees and J. Smolik regarding the substance of the May 28, 1998 meeting with Dr. Wolf, further including Mr. Smolik’s handwritten response affirming that any discussion of PH-10 was in the context of a PDT agent with no mention of potential use as a radiopaque or radiosensitizer agent, etc.
31. Feb 14, 2000 Dr. Dees’ response to Dr. Wachter re the meeting of May 28, 1998 with Dr. Wolf.
32. Feb 15, 2000 Dr. Wolf response to Dr. Scott letter of 14 Feb, wherein:
 - a. In the 2nd paragraph, Dr. Wolf asserts that Photogen has been “promptly informed of intellectual property and reduction to practice in [Wolf’s] laboratories at the MGH...”²⁰
 - b. In the 3rd paragraph, Dr. Wolf implies that Photogen has a responsibility to inform him and MGH of any inventions by Photogen.²¹
 - c. In the 4th paragraph, Dr. Wolf expresses concern that Photogen’s “**filings may not represent the earliest inventive step nor who actually was the inventor**” and that “key reductions to practice” occurred in his labs at MGH.

²⁰ While Photogen has documentation of various reductions to practice (under Photogen’s technical direction), Photogen was not made aware of any such information re possible invention by Dr. Wolf. Between the time that the Photogen-MGH Research Agreement commenced and July 1, 1999 when Dr. Wolf became a Photogen employee, Photogen received no reports of MGH or joint inventions from either Dr. Wolf or MGH, as stipulated under the terms of the Photogen-MGH Research Agreement. Only after July 1, 1999 did Dr. Wolf submit his first invention disclosure to Photogen (covering work done as a Photogen employee).

²¹ Photogen does not understand that it ever had any duty to advise Dr. Wolf of Photogen’s inventions. It is unclear what basis Dr. Wolf may have for such an assertion.

- d. In the 5th paragraph, Dr. Wolf requests joint review by Photogen, MGH and Nycomed.
 - e. In the 6th paragraph, Dr. Wolf notes that he has loyalties and responsibilities to Photogen, MGH and Nycomed.
33. Feb 25, 2000 E. Manzo letter to Dr. Wolf requesting evidence of the “earliest inventive step” as contemplated in Dr. Wolf’s letter of Feb. 15 and further requesting “any explanation of inventorship.”
34. Feb. 28, 2000 Dr. Wolf’s response to E. Manzo letter of 25 Feb. Dr. Wolf raises a number of points:
- a. **Dr. Wolf (erroneously) believes that the issue is conception of intratumoral injection of radiodense materials for purpose of improving radiation therapy.**
 - b. Dr. Wolf contends that work by MGH and Nycomed, both research results and patent filings, is “pretty thorough” in the field of radiosensitizers, and they had actual tests of many concepts.
 - c. Dr. Wolf asserts, “the MGH would insist that this data [presumably the data discussed in item #1] belongs to them and must not be used without their permission.”
 - d. Dr. Wolf notes that Photogen has declined to give him access to early IP filings (but states no reason why he is entitled to them).
 - e. Dr. Wolf alleges that Photogen and its counsel “participated actively in the review of the MGH and Nycomed filings and even insisted that MGH data not be used in support of MGH’s own filings” [emphasis added].²²
 - f. Dr. Wolf’s name was listed on Photogen “continuation filings.”²³ He reports interest (but he does not say by whom) in including MGH data in these filings, and he avers that would strengthen all the previous applications. There is some overlap of claims and a “less than open process of sharing these with collaborators in a timely fashion.”

²²This presumably refers to attempts by Dr. Wolf and/or P. Fasse in Oct 1999 to include in MGH / Nycomed PCT filings Photogen’s discovery of using Rose Bengal as a radiosensitizer for treatment and imaging, for example. After Photogen objected to such inclusion of Photogen’s discovery, MGH removed the proposed inclusion.

²³ The documents at issue were mere early internal drafts, not PTO filings, for other prospective patent applications. Dr. Wolf’s name was subsequently removed before filing any such application with the PTO.

- g. Dr. Wolf urges “combining such inventions as may have been made into a common technology platform.”²⁴ Among other things, Dr. Wolf admits that “the claims to radiosensitization have been made in prior art ...” This appears to concern claims in his MGH patent application.
- h. Dr. Wolf suggests that any concerns are ultimately between MGH and Photogen.
35. March 7, 2000 Dr. Wolf memo to E. Manzo urging that Manzo has incomplete information on inventorship and proposing to meet to compare notes. A record of the meeting could then be shared with MGH and Nycomed.
36. March 8, 2000 E. Manzo response letter to Dr. Wolf stating that MGH must be involved in any resolution of rights that could belong to MGH – hence, Photogen will deal directly with MGH. Manzo also informs Dr. Wolf that he is required, per his employment agreement, to disclose any inventions made subsequent to his employment with Photogen, and requests such records. (Apart from two Photogen invention disclosures received this year, no further records re Rose Bengal have, to date, been provided to Photogen by Dr. Wolf.)
37. March 9, 2000 Dr. Wolf response to E. Manzo letter of 8 Mar, agreeing that “the issues of multiple filings in the radiosensitization field should be jointly resolved by MGH and Photogen.” Dr. Wolf states that he cannot disclose records of Rose Bengal experiments conducted at MGH, which (according to Dr. Wolf) should be disclosed (only) at their discretion. He refuses to agree to produce records even from work subsequent to his employment by Photogen.
38. March 9, 2000 M. Murphy letter to Dr. Wolf instructing him not to contact MGH on behalf of Photogen and to send records regarding Rose Bengal + ionizing radiation after July 1, 1999 (the date when Dr. Wolf became a Photogen employee, according to the employment agreement -- see attachments to Exh. 1).
39. March 10, 2000 Dr. Wolf memo to M. Murphy, noting that data collected at MGH was performed while he served as Principal Investigator. Dr. Wolf implies that there may be infringement issues relevant to Photogen’s license with MGH, and requests notification if either party is considering legal action against him.
40. April 10, 2000 E. Manzo letter to Iain Miller (of MGH) regarding the Dr. Wolf situation. Manzo states that he has examined relevant Photogen records, believes there is no basis for Dr. Wolf’s concerns (although these are still unclear), notes that Photogen has no obligation to disclose its own inventions to Dr. Wolf, states that Dr. Wolf’s name was not on any application filed with the PTO, (again) requests disclosure by MGH and Dr. Wolf (as

²⁴ To Dr. Wolf, a “common technology platform” evidently meant listing him as a joint inventor on Photogen’s early discoveries, rather than assembling a portfolio of patents with correct inventorship on each, determined on the basis of who contributed to the conception of the subject matter specified in the claims.

required in the Research Agreement), and states, **"If MGH now considers that there is a proper basis to name Dr. Wolf as a co-inventor, please set forth a cogent explanation of the facts for our consideration."**²⁵

41. April 20, 2000 Dr. Dees memo to Dr. Wolf, stating, "You mentioned data I haven't seen. I need to see all information we have...."
42. April 20, 2000 Dr. Wolf response to Dr. Dees memo of 20 Apr. Dr. Wolf states, "I wish that I could comply, but that is all in the hands of the lawyers for now."
43. April 24, 2000 Dr. Dees memo to Dr. Wolf, making another demand for data being withheld by Dr. Wolf: "I would like to request again for any data on Rose Bengal. As mandated by Photogen's Research Agreement with MGH and your Employment Agreement, you are required to provide all data collected under these agreements promptly to [Photogen]."
44. April 24, 2000 Dr. Wolf response to Dr. Dees memo of 24 Apr. Dr. Wolf states, "If you can get Manzo et al and MGH to allow me to disclose my data obtained while employed by Photogen and doing sponsored Photogen research at MGH, I would be happy to disclose what I have learned. The funded period does not correspond to the research results."
45. April 24, 2000 Dr. Dees response to Dr. Wolf memo of 24 Apr. Dr. Dees asks, "Does this mean you had Rose Bengal radiosensitizer research results at MGH before funding started approximately Oct. 1998. Manzo has already said that the data under Photogen employment should be given to us."
46. April 24, 2000 Dr. Wolf response to Dr. Dees memo of 24 Apr. Dr. Wolf states, **"We began radiosensitizer research at MGH even before Photogen was formed. We continued to do radiosensitizer research at MGH after the sponsored research agreement expired."**²⁶
47. April 25, 2000 Dr. Scott memo to Dr. Wolf requesting withheld data on Rose Bengal – this is at least the fifth request for this information from or on behalf of Photogen.
48. April 26, 2000 Dr. Wolf memo to Dr. Scott. He agrees that Photogen has unquestioned ownership of "numerous claims" but then refers to patent filings or licensing. He says MGH does not have a complete record of Dr. Wolf's work in the field, and he retrieved from storage all MGH lab notebooks and CT log books, which are in Dr. Wolf's Westboro office and available for Photogen lawyers to inspect.

²⁵ MGH never answered this letter with any written explanation of why its employee Dr. Wolf is entitled to be named as a co-inventor.

²⁶ Dr. Wolf notably failed to respond to the question of whether he conducted radiosensitizer work *on Rose Bengal* (or any other halogenated xanthene) prior to the start of the Research Agreement with Photogen.

49. April 26, 2000 T. Grippo letter to Iain Miller (MGH) regarding a telephone conference about Dr. Wolf's materials. Dr. Wolf is to provide all records from July 1, 1999 (the date of his Photogen employment) to E. Manzo; all earlier materials are to be provided to MGH.
50. April 27, 2000 Dr. Wolf letter to T. Grippo. Dr. Wolf says that he can't provide all relevant documents because he doesn't know what is relevant and repeats statement that it would have been better if the lawyers hadn't become involved.²⁷
51. May 2, 2000 Dr. Wolf memo to T. Grippo and P. Fasse. To begin review process, Dr. Wolf requests permission to allow P. Fasse (patent counsel for MGH) to see all Photogen patent files in Dr. Wolf's possession.
52. May 4, 2000 Dr. Wolf memo to T. Grippo. Dr. Wolf comments on Photogen filings in his possession, noting that example data in [another Photogen patent application referred to as PHO-120] was collected at MGH, but ignoring the issue of Photogen's ownership of such data under the Research Agreement and Photogen's right to an exclusive license in any resulting invention.) **Dr. Wolf mentions his role in reduction to practice, refers to "radiosensitization inventorship" and "important inventorship issues,"** and reiterates that his notebooks are available for inspection (but only in Westboro, MA).²⁸ Dr. Wolf says he will not participate in the resolution process if he cannot be advised on what his legal and employment obligations are.
53. Dees *et al.* U.S. Patent No. 4,599,227 issued July 8, 1986
54. Brown *et al.* U.S. Patent No. 5,128,139 (Brown, Ward, Dees) issued July 7, 1992
55. Kolobanov *et al.* U.S. Patent No. 4,973,848 issued November 27, 1990
56. Williams *et al.* U.S. Patent No. 5,576,013 issued November 19, 1996
57. Chen U.S. Patent No. 5,827,186 issued October 27, 1998
58. Fisher *et al.*, "Clinical and Preclinical Photodynamic Therapy", Lasers In Surgery and Medicine, vol. 17, p. 2-31, 1995
59. Amended Complaint, *Photogen v. Gerald L. Wolf and The General Hospital Corp.*

²⁷ Compare Dr. Wolf's comments here with his request to Dr. Scott for an independent review (Feb 7, 2000).

²⁸ Note that Photogen's head office at that time was in Tennessee.

60. October 13, 1998 John Smolik (Photogen) letter to Dr. I. Miller of MGH expressing interest by Photogen in licensing of patent rights on Dr. Wolf's invention.

The documents reflect an ever-widening schism between Dr. Wolf and Photogen on inventorship and other issues, along with Photogen's repeated efforts to have Dr. Wolf abide the terms of his employment agreement and the research agreement among Photogen, Dr. Wolf, and MGH. Photogen had considered various hypotheses that Dr. Wolf might have on inventorship of the method claims, but he has now acknowledged in his December 4, 2000 statement that he claims no role in claim 1 of this application.

The named inventors Dees, Scott, Smolik, and Wachter believe that they are the true and correct inventive entity. On the basis of the law applied to the evidence known to Photogen at present, no correction of inventorship is thought to be required. The PTO is requested to review these submissions thoroughly.

Should any questions arise, the undersigned will be pleased to attend an interview with the Examiner, and one or more of the named joint inventors will also be present.

Respectfully submitted,



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Enclosures 1-60 (as listed)